

Hepatitis B & C Diagnosis & Treatment Case Studies

Hepatitis: The Silent Epidemic in Kentucky
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Disclosures

Jens Rosenau, MD, has disclosed that he has received consulting fees from Merck and Vertex.

The slides will discuss uses and dosages for therapeutic products that have not been approved by the United States Food and Drug Administration.

Hepatitis C

The background of the slide is a dark green gradient. A horizontal band of a slightly lighter green color spans the middle, where the title is located. In the bottom right corner, there is an abstract graphic consisting of several overlapping, wavy, translucent green shapes that create a sense of depth and movement.

1942 1943 1944 1945 1946 1947 1948 1949 1950 1951 1952 1953 1954 1955 1956 1957 1958 1959 1960 1961 1962 1963 1964 1965 1966 1967

BORN FROM 1945 TO 1965?

**AMERICANS BORN DURING THESE YEARS HAVE
THE HIGHEST RATES OF HEPATITIS C.**

Talk to your doctor about getting tested. Early detection can save lives.



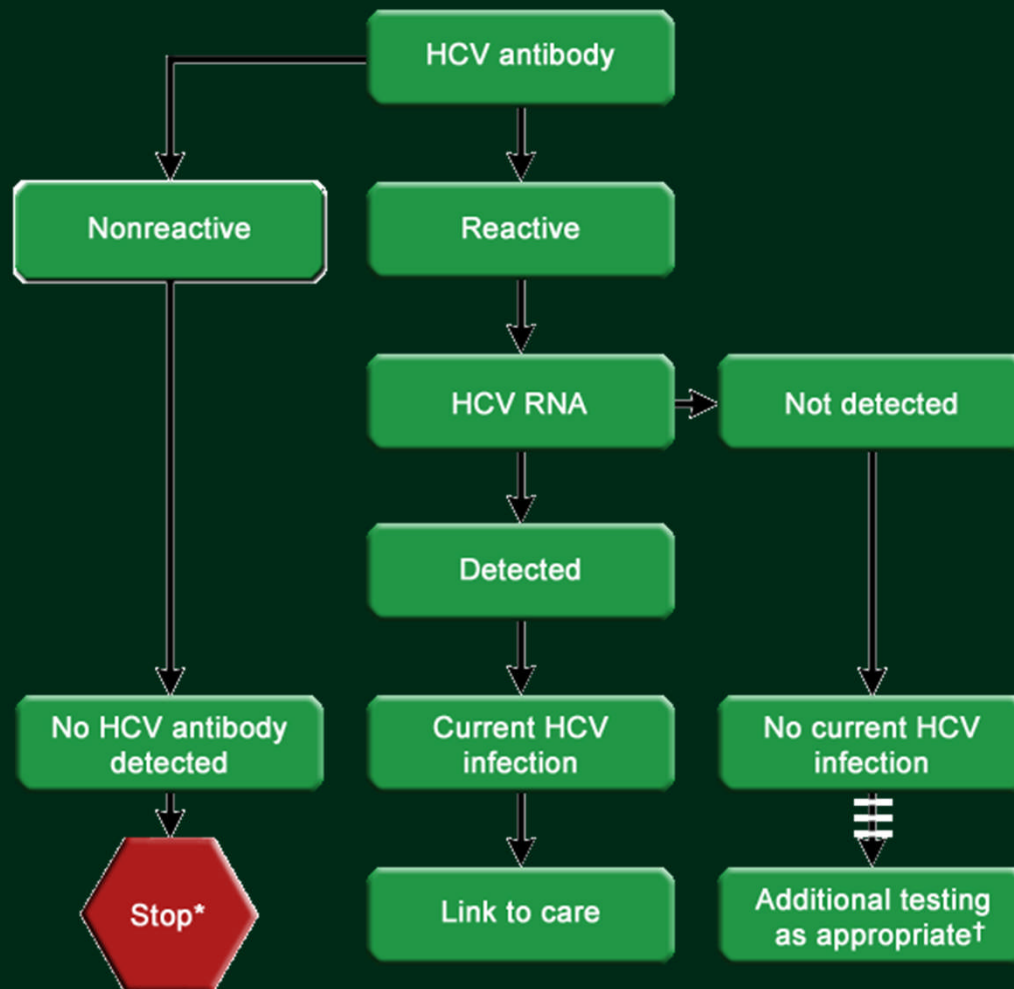
U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention

www.cdc.gov/knowmorehepatitis



**KNOW
MORE
HEPATITIS™**

HCV Testing and Linkage to Care



CDC Recommendation

Evaluation by a practitioner who is prepared to provide comprehensive management, including consideration of antiviral therapy, is recommended for all persons with current (active) HCV infection.

AASLD/IDSA Guidelines
www.hcv-guidelines.org

Case 1:

- 55 yo white male referred for evaluation for HCV treatment
- He feels well
- Risk factors: IDU 20+ yrs ago; no recent use
- Minimal alcohol use: 2-3 beers/wk
- No significant PMSH
- Exam: normal

Case 1: Genotype 1, Interferon eligible

- | | | | |
|-----------------|---------|----------------------------|----------------|
| ■ Total protein | 6.7 | ■ HCV RNA | 1,345,789 IU/L |
| ■ Albumin | 4.3 | ■ Genotype 1a | |
| ■ Creatinine | 1.1 | ■ HBsAg | NEG |
| ■ Bilirubin | 0.9 | ■ HBsAb | POS |
| ■ AST | 54 | ■ Total HAV Ab | NEG |
| ■ ALT | 68 | | |
| ■ ALP | 97 | ■ Ultrasound: normal liver | |
| ■ Hemoglobin | 12.3 | | |
| ■ WBC | 3.2 | | |
| ■ Platelets | 189,000 | | |
| ■ Anti-HCV | POS | | |

How Would You Assess Liver Histology?

- All patients should be staged to determine if they are cirrhotic
 - Cirrhotics have somewhat reduced likelihood of SVR with current therapies, but this will likely improve with future regimens
 - Cirrhotics need HCC screening
- Role of biopsy
 - Few experts are performing biopsy on a regular basis
 - Reserved for when other methods provide insufficient information
- Most experts initially stage with serum panel, such as APRI or FIB-4
 - FIB-4 provides simplicity of assessment [age, AST, ALT, platelets]
- Some experts also use Fibroscan, as it can be conducted right in the office

Case 1: Fibrosis Assessment

- APRI score 1.2 Low risk of advanced fibrosis
 - FIB 4 score 1.49 Indeterminant for advanced fibrosis
 - Liver biopsy Stage 1 to 2 fibrosis (Metavir)
-
- Currently, evaluating fibrosis/cirrhosis status can inform the decision to treat now or wait for an all-oral treatment
 - In a patient with minimal disease and no complications, the preferred strategy is to wait for better treatment options
 - Physicians should discuss the options with each patient and arrive at a decision together

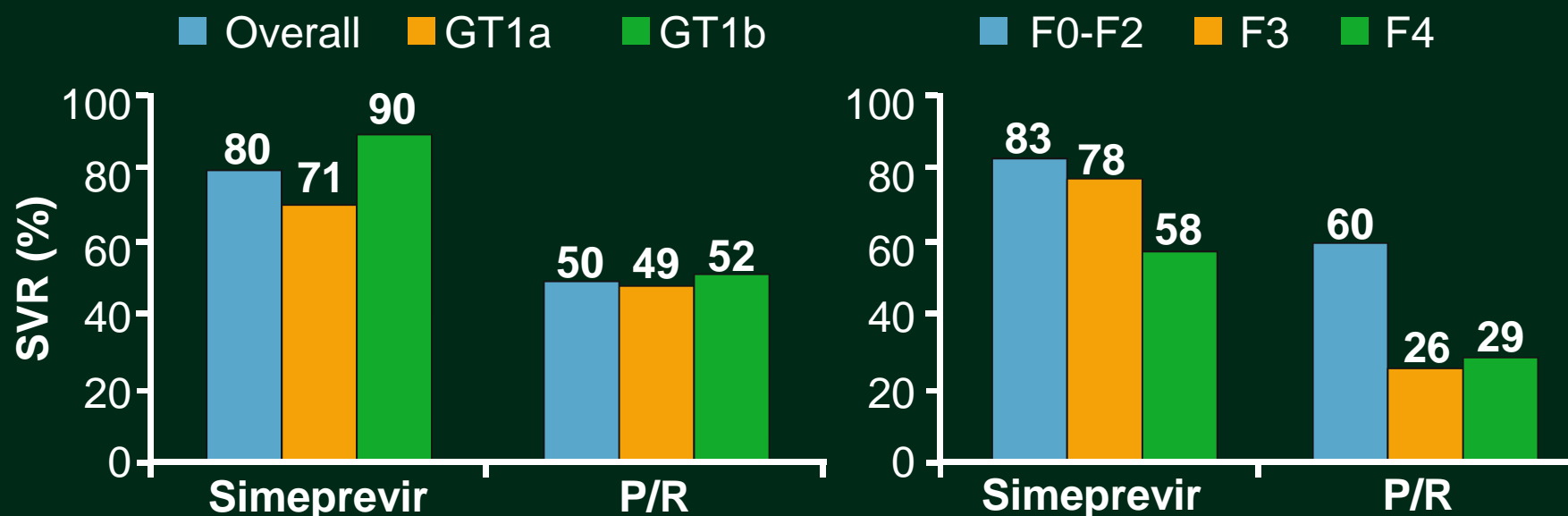
Available HCV Therapies for Genotype 1 Key Data

Antiviral Therapies for Genotype 1 Currently Available

Regimen	DAA Class
PegIFN + RBV	None
PegIFN + RBV + boceprevir	Protease inhibitor
PegIFN + RBV + telaprevir	Protease inhibitor
PegIFN + RBV + simeprevir	Protease inhibitor
PegIFN+ RBV + sofosbuvir	Nucleotide analogue NS5B polymerase inhibitor
RBV + sofosbuvir* (Extended duration)	Nucleotide analogue NS5B polymerase inhibitor
Sofosbuvir + simeprevir	NUC + PI (off-label)

*Sofosbuvir + ribavirin for 24 wks can be considered in patients with genotype 1 HCV who are ineligible for interferon.

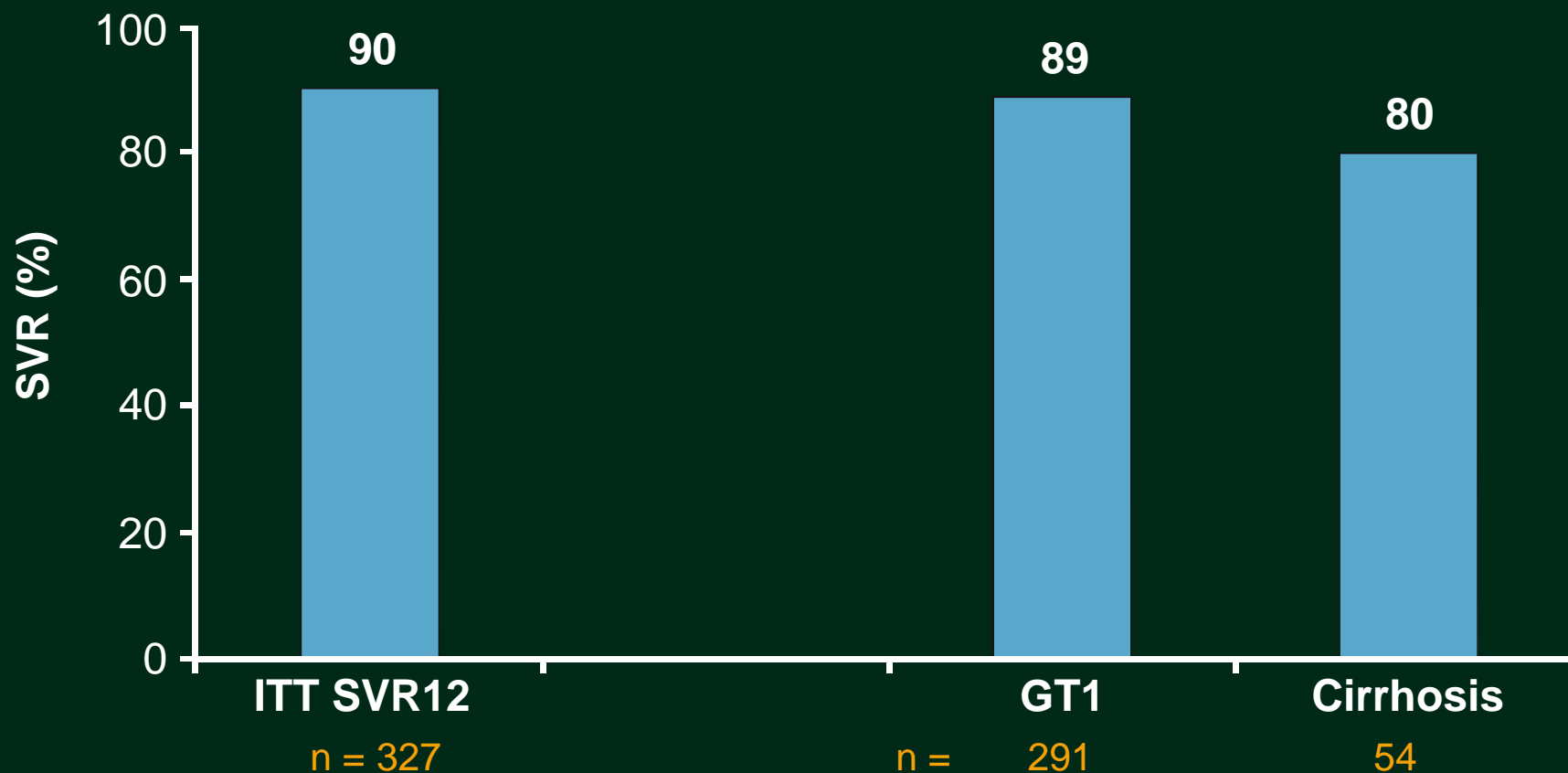
Simeprevir + P/R: Phase III QUEST-1: Impact of Subtype & Fibrosis Stage in GT1



- SVR: GT1b > GT1a
- SVR: F0-F2 > F4
- SVR is lowest for patients with GT1a and baseline Q80K mutation

NEUTRINO Study: Virologic Response

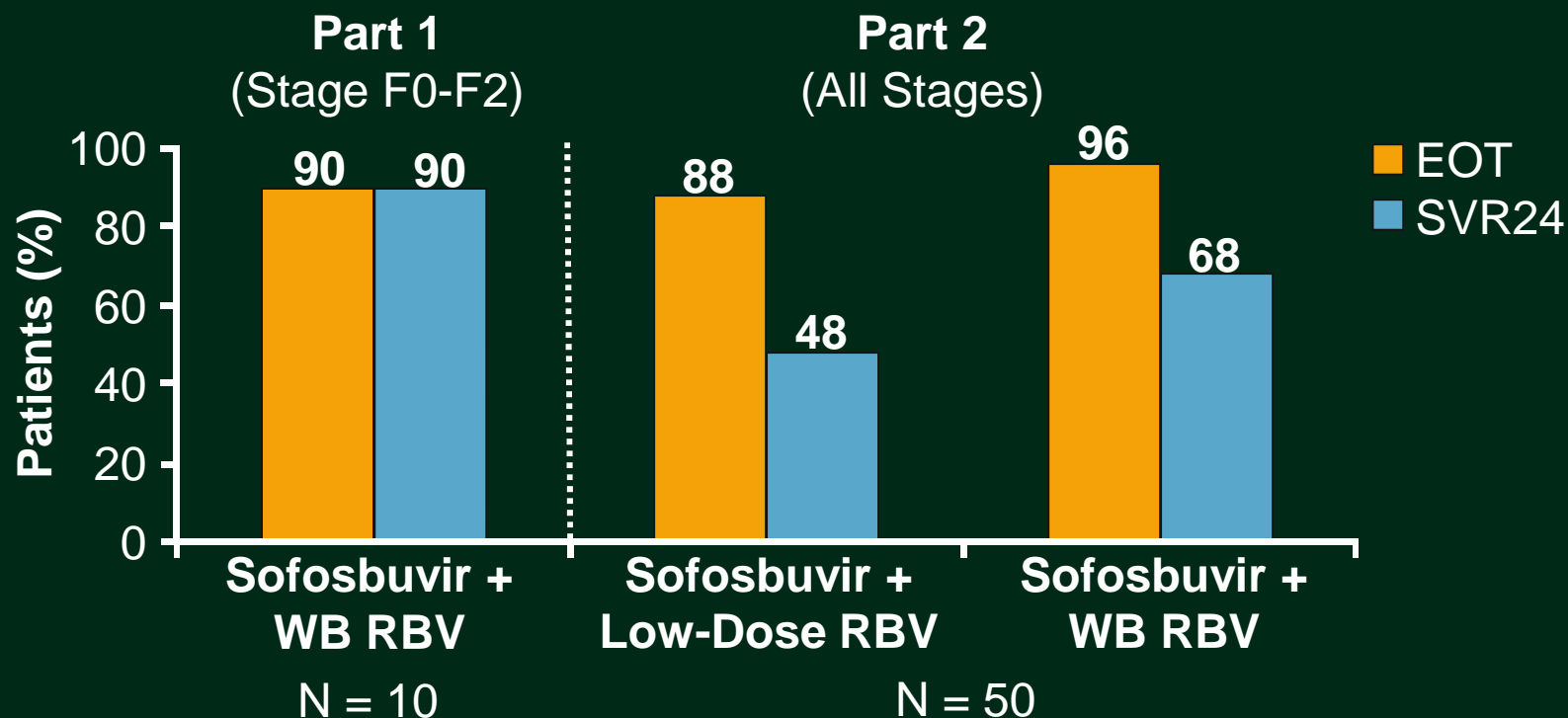
Sofosbuvir + PegIFN/RBV x 12 Wks



Lawitz E, et al. N Engl J Med. 2013;368:1878-1887.

NIH SPARE Study (No Interferon): Sofosbuvir + RBV in HCV GT1–Infected Pts

- 24 wks sofosbuvir + WB or low-dose (600 mg) RBV in treatment-naïve subjects
- Primarily GT1a (70%), male (66%), black (83%), *IL28B* CT/TT (81%)
- Advanced liver disease 23%; median BMI ranged from 26-30; high median HCV RNA

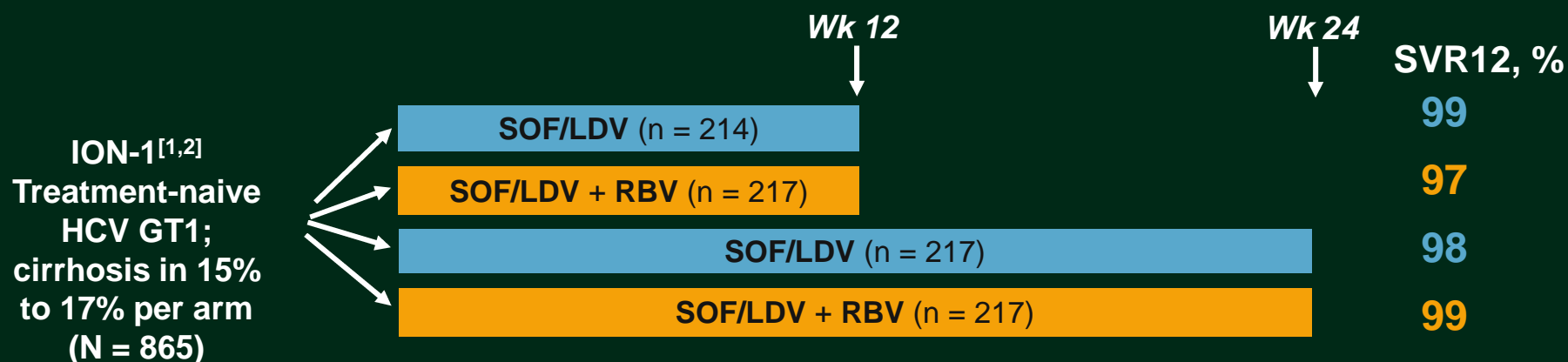


Osinusi A, et al. JAMA. 2013;310:804-811.

Key Factors in Deciding to Treat or Wait

- Patient factors
 - Urgency to treat
 - Likelihood of response
 - HCV genotype
 - Treatment experience
 - IL28B genotype
 - Degree of fibrosis
 - Patient motivation
- Treatment factors
 - Efficacy of current options
 - Safety of current options
 - Duration of therapy
 - Pill burden, dosing frequency
 - Future options and their timelines

Phase III Studies of SOF/LDV FDC \pm RBV for 12 or 24 Wks in GT1 Patients



- ION-1,2: No difference in outcomes according to cirrhosis status, type of treatment failure

1. Mangia A, et al. EASL 2014. Abstract O164. 2. Afdhal N, et al. N Engl J Med. 2014;370:1889-1983.
3. Afdhal N, et al. N Engl J Med. 2014;370:1483-1493.

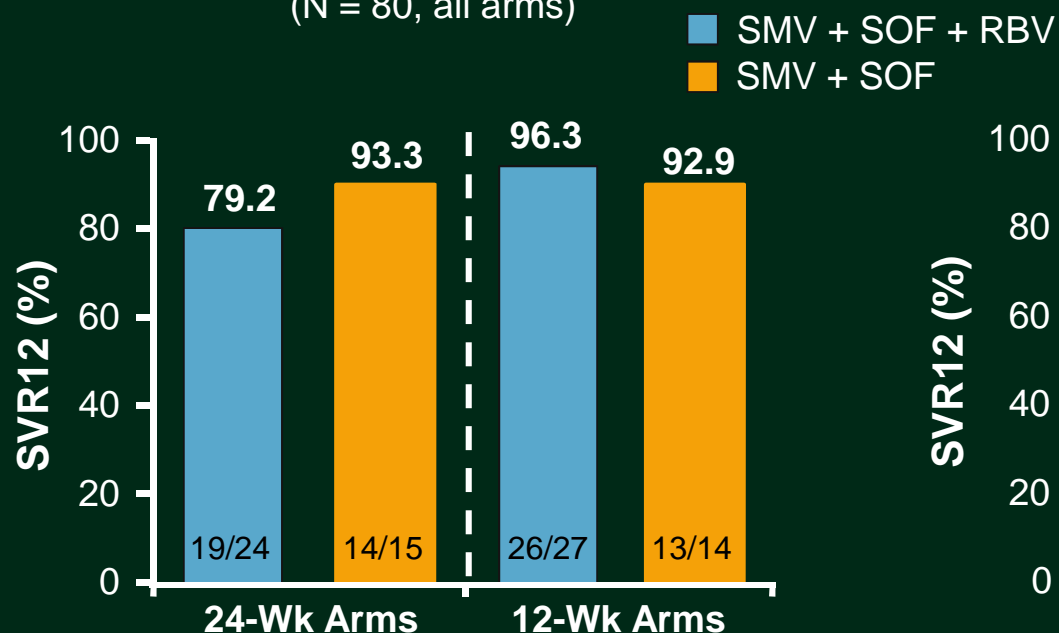
Case 2: Genotype 1b, compensated cirrhosis, IFN ineligible

- 55 yo Caucasian female
- H/o IDU 30 y ago, history of heavy alcohol use in her 30s, multiple nonprofessional tattoos
- Genotype 1b, HCV RNA 4,550,000 IU/mL
- ALT 55 U/L, AST 80 U/L, Platelets 65,000/mm³
- Albumin 2.9 g/dL, Bilirubin 1.7 mg/dL, INR 1.3
- U/S: Nodular liver surface, splenomegaly 16 cm, no ascites
- EGD: grade 1 EV, PHG, denies h/o GI bleeding

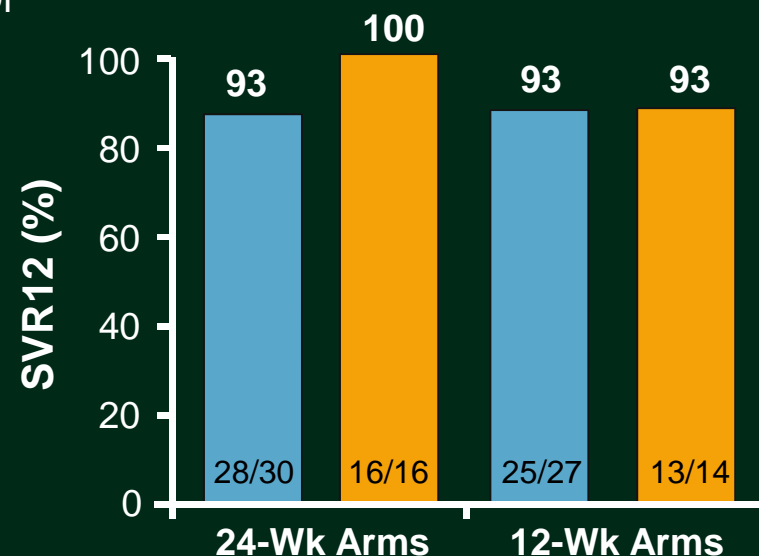
Summary: Compensated Child A cirrhosis

Combination of Sofosbuvir (NUC) and Simeprevir (PI): COSMOS

Cohort 1 (F0-F2 Nulls): SVR12
(N = 80, all arms)



Cohort 2 (F3-F4 Naives/Nulls): SVR12
(N = 87, all arms)



- Relapse in 3 pts in cohort 1 and 3 pts in cohort 2; all with GT1a and GT2 with Q80K polymorphism at baseline
- AEs (anemia and indirect bilirubin increases) largely confined to RBV arms
- SVR in patients with GT1a and Q80K+ = 88% to 100%

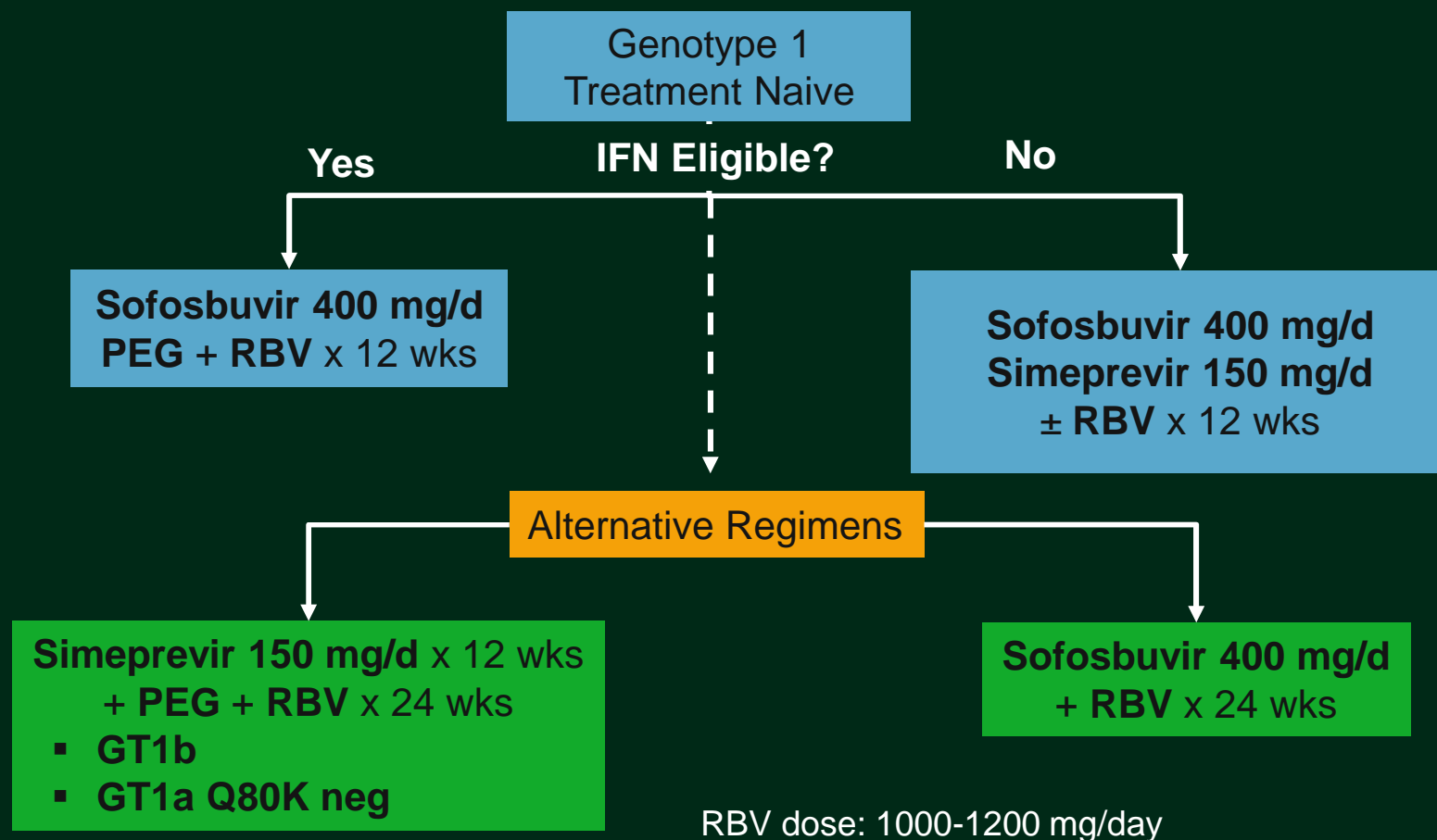
Jacobson I, et al. AASLD 2013. Abstract LB-3. Lawitz E, et al. EASL 2014. Abstract 165.

Adverse Effects of New Therapies

- PegIFN/RBV: well-established AE profiles
- Sofosbuvir^[1-3]
 - Mild fatigue
 - Mild headache
- Simeprevir^[4,5]
 - Mild, reversible hyperbilirubinemia
 - Due to transporter inhibition and not associated with hepatotoxicity
 - Mild photosensitivity

1. Lawitz E, et al. N Engl J Med. 2013;368:1878-1887. 2. Jacobson I, et al. AASLD 2013. Abstract LB-3.
3. Sofosbuvir [package insert]. 4. Fried MW, et al. Hepatology. 2013;58:1918-1929. 5. Simeprevir [package insert].

AASLD/IDSA Recommendations for HCV Genotype 1 Treatment-Naive Patients

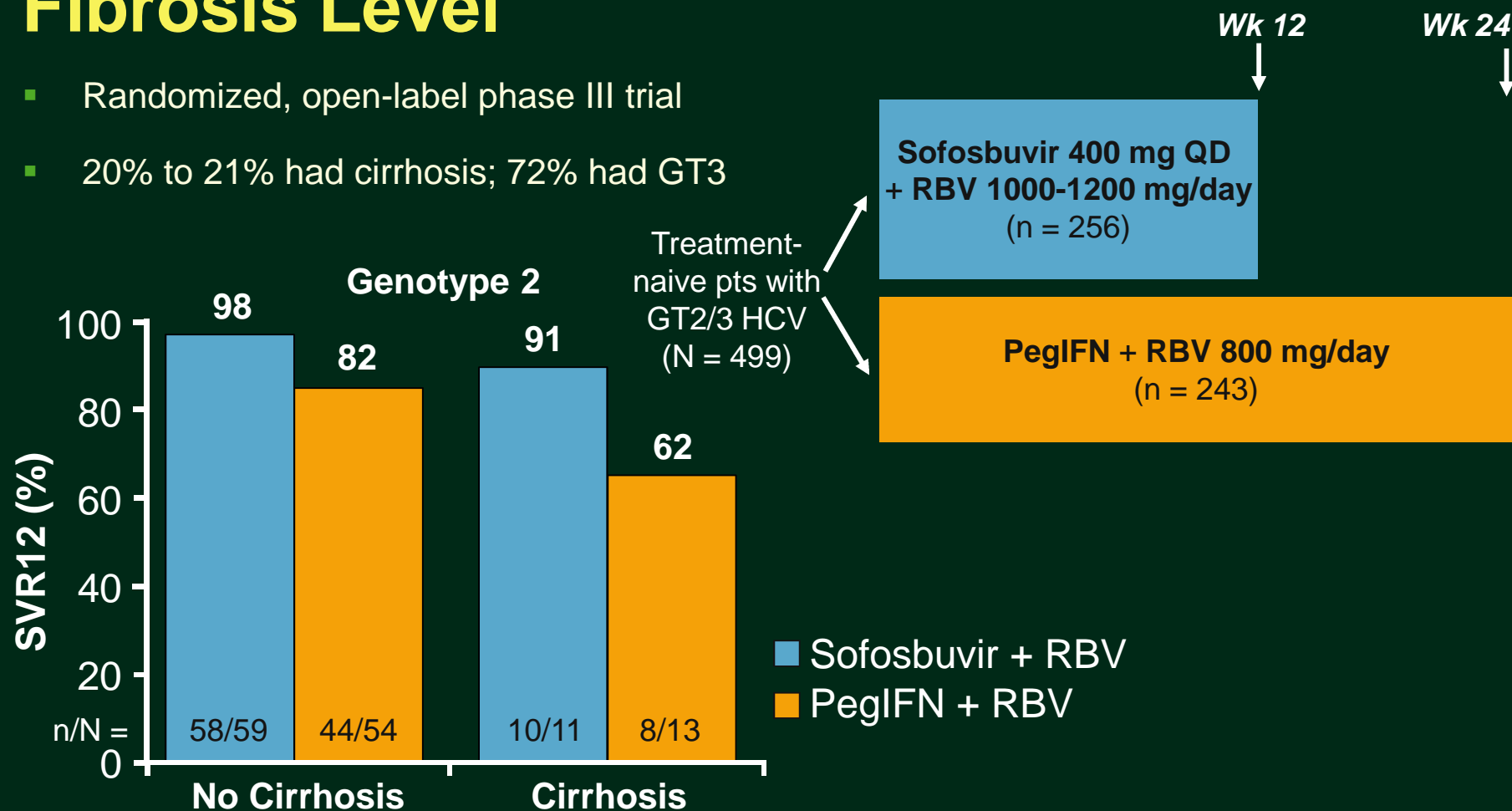


Case 3: Genotype 2, IFN eligible with recent infection

- 23 yo F referred for HCV treatment, diagnosed 2 y ago
- H/o brief episode of IDU about 3 y ago
- New partner for 1 year, recently married, planning pregnancy
- Has heard about bad side effects of treatment, but wants to get rid of the infection
- Labs: ALT 35, AST 25, Platelets 285,000/mm³
- HCV RNA 1,250,000 IU/mL, Genotype 2
- U/S Abdomen: Normal.

FISSION: SVR12 in Genotype 2 Patients by Fibrosis Level

- Randomized, open-label phase III trial
- 20% to 21% had cirrhosis; 72% had GT3



AASLD/IDSA Recommendations for Genotype 2 HCV Treatment-Naive Pts

Population	Recommended Regimen	Duration
Treatment naive and previous relapsers, genotype 2	Sofosbuvir 400 mg + RBV 1000-1200 mg/day	12 wks

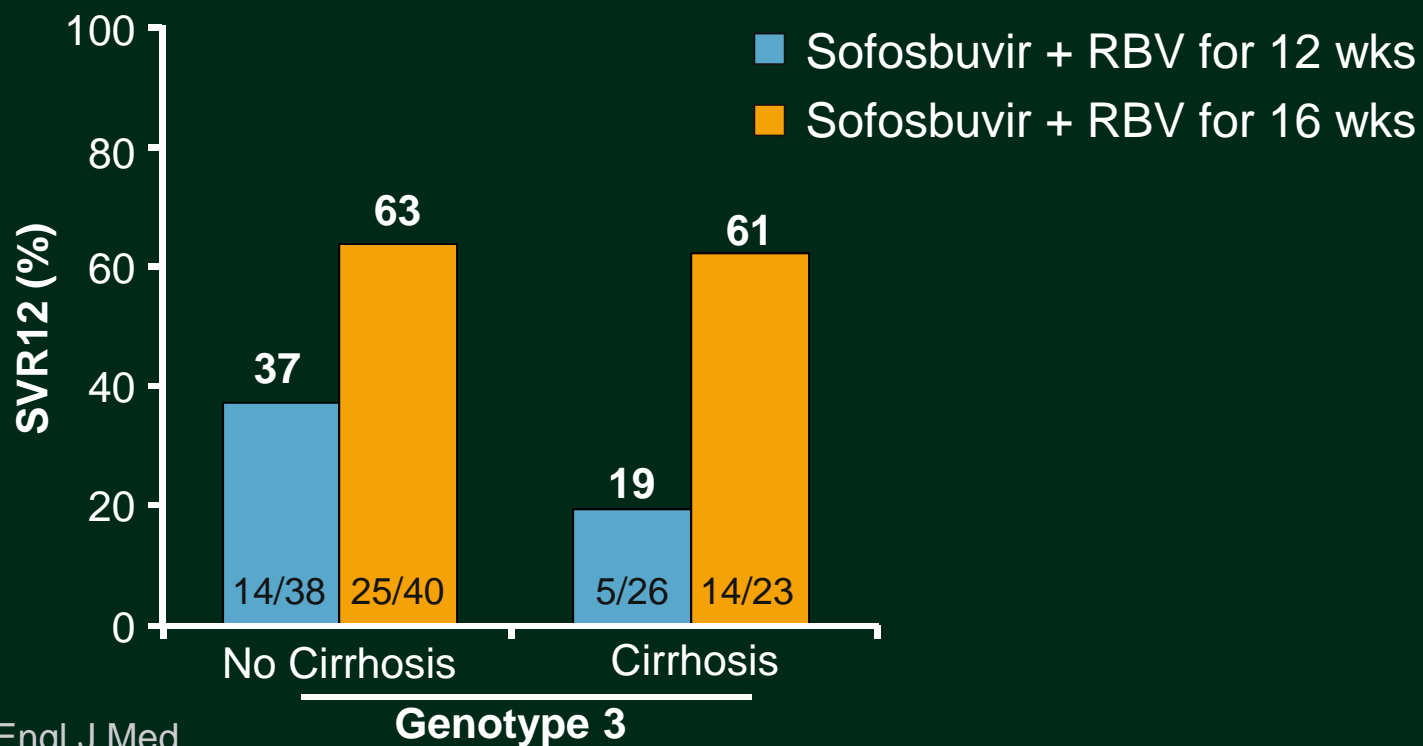
- Alternative regimens: none
- Regimens specifically not recommended:
 - PegIFN/RBV x 24 wks
 - Monotherapy with pegIFN, RBV, or DAA
 - TVR-, BOC-, SMV-based regimens

**Is Genotype 3 as easy to treat as
genotype 2?**

Key Data

FUSION: SVR12 With Sofosbuvir + RBV by Genotype and Fibrosis Level

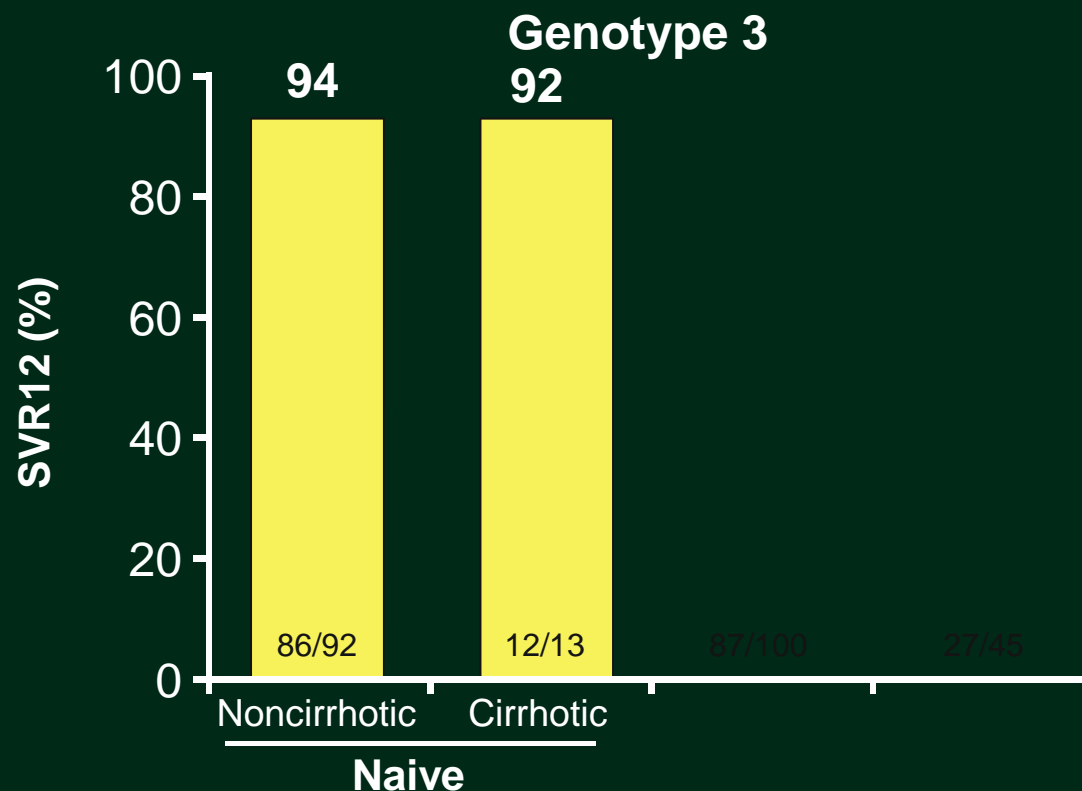
- Randomized, double-blind phase III trial
 - 62% to 64% had GT3 HCV; 33% to 35% had cirrhosis; 75% to 76% were previous relapsers



Jacobson IM, et al. N Engl J Med.
2013;386:1867-1877.

VALENCE: Sofosbuvir + RBV for 24 Wks in GT3 IFN-Naive/Ineligible/Tx Failures

- Phase III study in Europe
- Genotype 2/3, naive/experienced



Zeuzem S, et al. AASLD 2013. Abstract 1085.

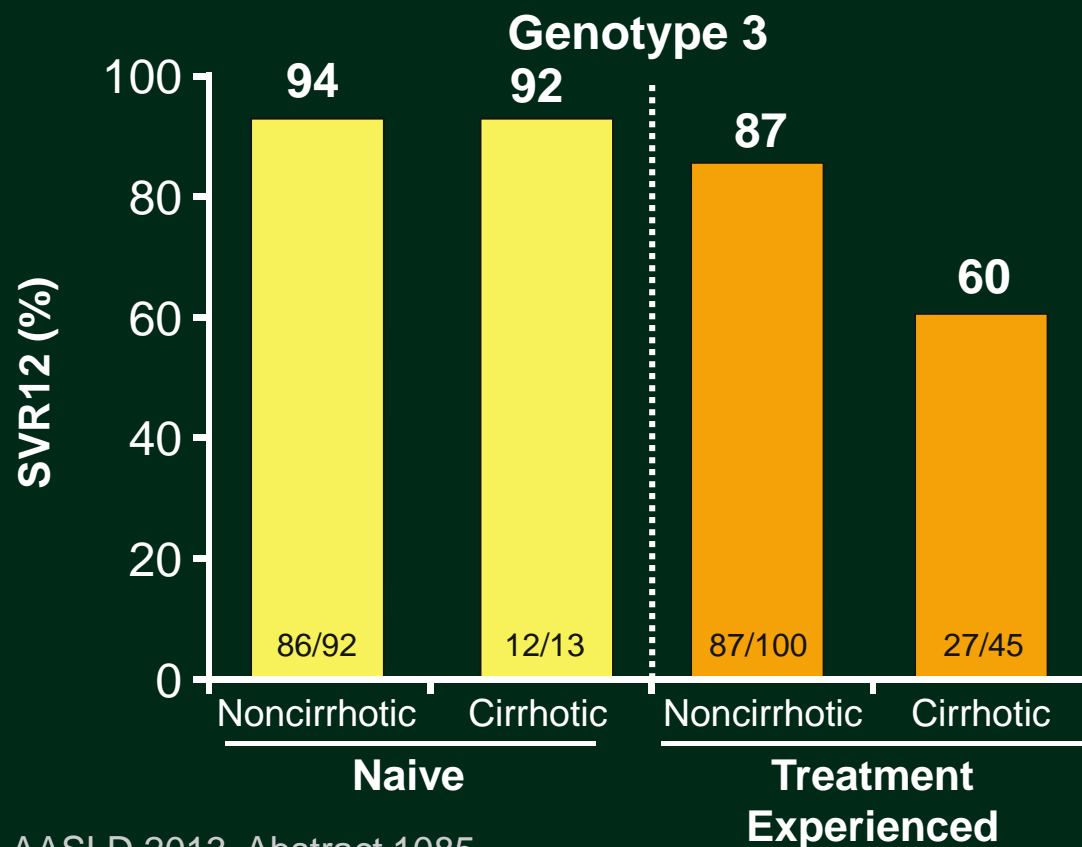
Case 4

Genotype 3, IFN eligible

- 61 yo Caucasian male
- H/o IDU >30 y ago, h/o significant alcohol use when young
- Liver cirrhosis, biopsy proven
- Focal 1,7 cm liver lesion, suspicious but not diagnostic for HCC
- Treatment experienced: Relapse x 3, last time after 72 weeks of pegIFN plus higher dose ribavirin
- ALT 43, bili 1.9, albumin 3.8, platelets 103,000

VALENCE: Sofosbuvir + RBV for 24 Wks in GT3 IFN-Naive/Ineligible/Tx Failures

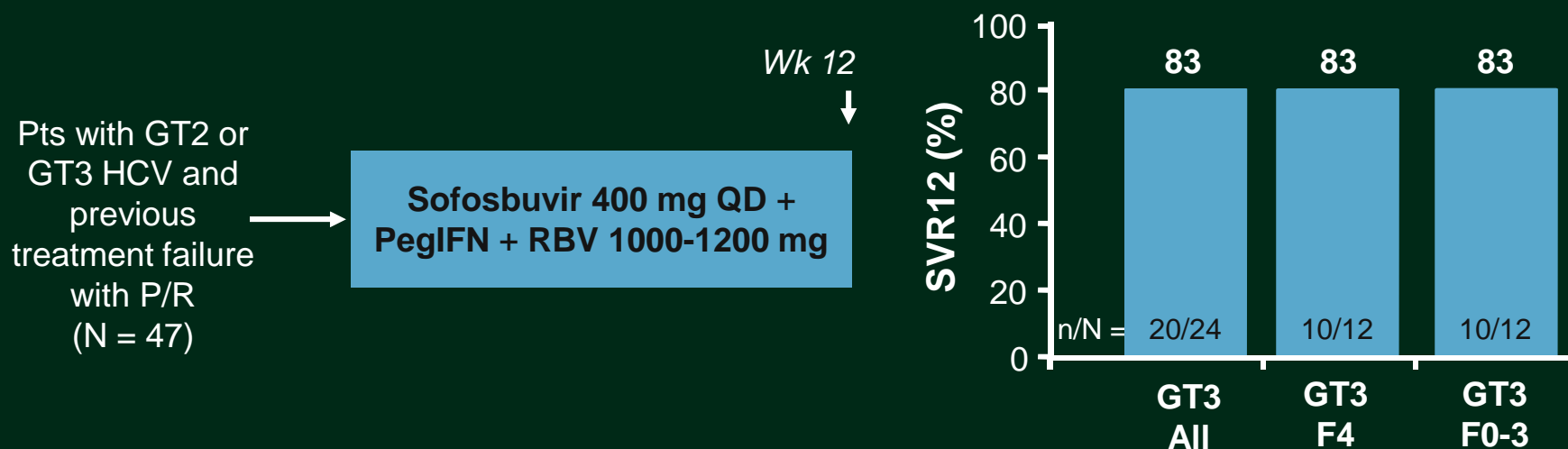
- Phase III study in Europe
- Genotype 2/3, naive/experienced



Zeuzem S, et al. AASLD 2013. Abstract 1085.

LONESTAR-2: Sofosbuvir + P/R for 12 Wks in Treatment-Experienced GT3 HCV Pts

- Single-arm trial of pts with treatment failure on P/R
- Approximately 50% with compensated cirrhosis



- Similar rates of SVR12 in pts with and without cirrhosis

AASLD/IDSA Recommendations for Genotype 3 HCV Treatment-Naive Pts

Population	Recommended Regimen	Duration
Regardless of IFN eligibility	Sofosbuvir 400 mg + RBV 1000-1200 mg/day	24 wks

Population	Alternative Regimen	Duration
Only consider if eligible for IFN	Sofosbuvir 400 mg + pegIFN + RBV 1000-1200 mg/day	12 wks

Not recommended:

- PegIFN/RBV for 24-48 wks
- Monotherapy with pegIFN, RBV, or a DAA
- Telaprevir, boceprevir, simeprevir

AASLD/IDSA Recommendations for Genotype 3 HCV Treatment-Experienced

Population	Recommended Regimen	Duration
Regardless of IFN eligibility	Sofosbuvir 400 mg + RBV 1000-1200 mg/day	24 wks

Population	Alternative Regimen	Duration
Consider only if eligible for IFN	Sofosbuvir 400 mg + pegIFN + RBV 1000-1200 mg/day	12 wks

Not recommended:

- PegIFN/RBV ± telaprevir, boceprevir, simeprevir
- Monotherapy with pegIFN, RBV, or a DAA

Treatment Summary (HCV all genotypes)

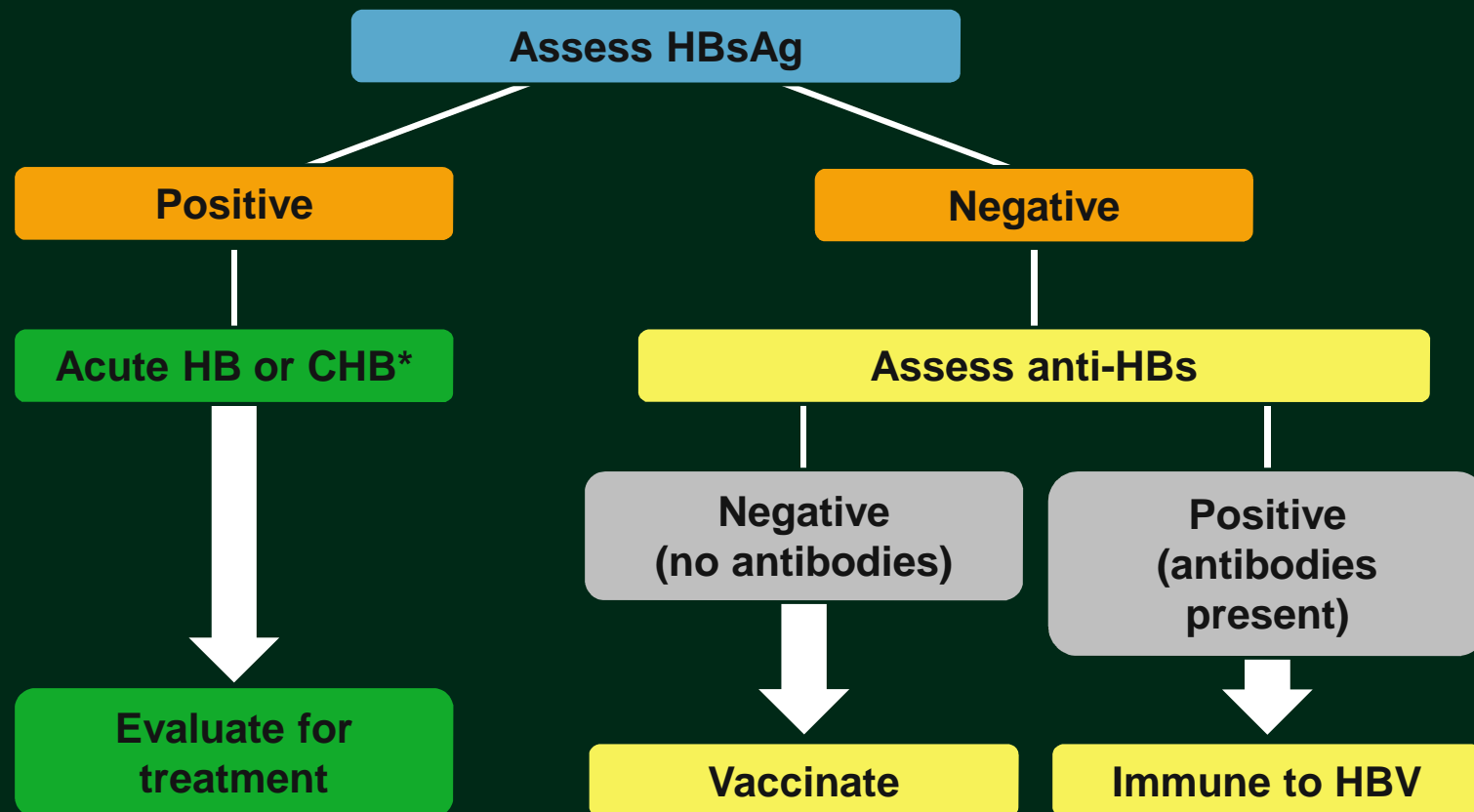
- SVR rates > 90% with currently available HCV therapies in treatment-naïve patients, even higher rates expected
- Treatment duration now shorter with 12 to 24 weeks; 8 to 12 weeks with IFN free DAA regimens expected
- Side effect profiles have improved with IFN free regimens and second wave of DAAs, expected to improve further
- Divergence between GT2 and GT3 with SOF + RBV
- Previous predictors of response such as viral load, race, IL28B status, fibrosis stage (?), losing clinical relevance
- More data needed for special patient populations such as decompensated cirrhotics, renal insufficiency, transplant

Hepatitis B



Initial Evaluation and Tests to Diagnose HBV

HBV Screening Algorithm



*Time from positive HBsAg test to diagnosis of CHB is 6 mos.

Keeffe EB, et al. Clin Gastroenterol Hepatol. 2008;6:1315-1341.

Hepatitis B Serology: First Phase Testing

- Total anti-HBc can be used as alternative; those testing positive should be tested for HBsAg and anti-HBs
 - Appears at the onset of symptoms in acute hepatitis and persists for life
 - Presence indicates **EXPOSURE** (previous or ongoing infection with HBV)

Hepatitis B Serology: IgM anti-HBc

- IgM anti-HBc (IgM antibody to hepatitis B core antigen)^[1]
 - Presence indicates acute infection (negative in chronic infection)
 - Positivity indicates recent infection with HBV (≤ 6 mos)
 - Occurs in the presence of acute exacerbation of *chronic* HBV disease

1. CDC. Hepatitis B FAQs for health professionals. Available at: <http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm>. 2. Colloredo MG, et al. Arch Virol Suppl. 1993;8:203-211.

Interpretation of Serologic Results

HBsAg	Total Anti-HBc	IgM Anti-HBc	Anti-HBs	Interpretation
Negative	Negative	NA	Negative	Susceptible; offer vaccination
Negative	Positive	NA	Positive	Immune due to natural infection
Negative	Negative	NA	Positive	Immune due to hepatitis B vaccination
Positive	Positive	Negative	Negative	Chronic HBV infection
Positive	Positive	Positive	Negative	Acute HBV infection/ Reactivation of Chronic HBV Infection
Negative	Positive	NA	Negative	Unclear; could be any one of the following: <ol style="list-style-type: none"> 1. Resolved infection (most common) 2. False-positive anti-HBc; susceptible 3. "Low-level" chronic infection 4. Resolving acute infection

Case 1: Acute Hepatitis B, non-severe

- 54 yo Caucasian female
- RUQ pain, nausea, fatigue
- Multiple sexual partners
- ALT 1,520 IU/mL, AST 1,230 IU/mL, ALP 220 IU/mL, Bilirubin 3.2 mg/dL, INR 1.0, Platelets 265,000/mm³
- HBsAg +, Anti-HBs -, Anti-HBc IgM +, Anti-HCV -
- HBeAg +, HBV DNA 365,000 IU/mL
- U/S: Hepatomegaly, no splenomegaly, no ascites, thickened GB wall, normal bile ducts

Case 1: Acute Hepatitis B, severe

- 54 yo Caucasian female
- RUQ pain, nausea, fatigue, has noticed worsening jaundice 1 week ago
- Multiple sexual partners
- ALT 1,520 IU/mL, AST 1,230 IU/mL, ALP 220 IU/mL, Bilirubin 17.2 mg/dL, INR 1.8, Platelets 265,000/mm³
- HBsAg +, Anti-HBs -, Anti-HBc IgM +, Anti-HCV -
- HBeAg +, HBV DNA 365,000 IU/mL
- U/S: Hepatomegaly, no splenomegaly, no ascites, thickened GB wall, normal bile ducts

Acute Hepatitis B

Treat only if severe, prevent acute liver failure

Severe:

- significant coagulopathy (INR > 1.5)
- prolonged high bilirubin (>4 weeks >10)

Definition of acute liver failure:

**Acute severe impairment of liver function
with icterus and coagulopathy**

No underlying chronic liver disease

Hepatic Encephalopathy

Case 2: Exacerbation of Chronic hepatitis B

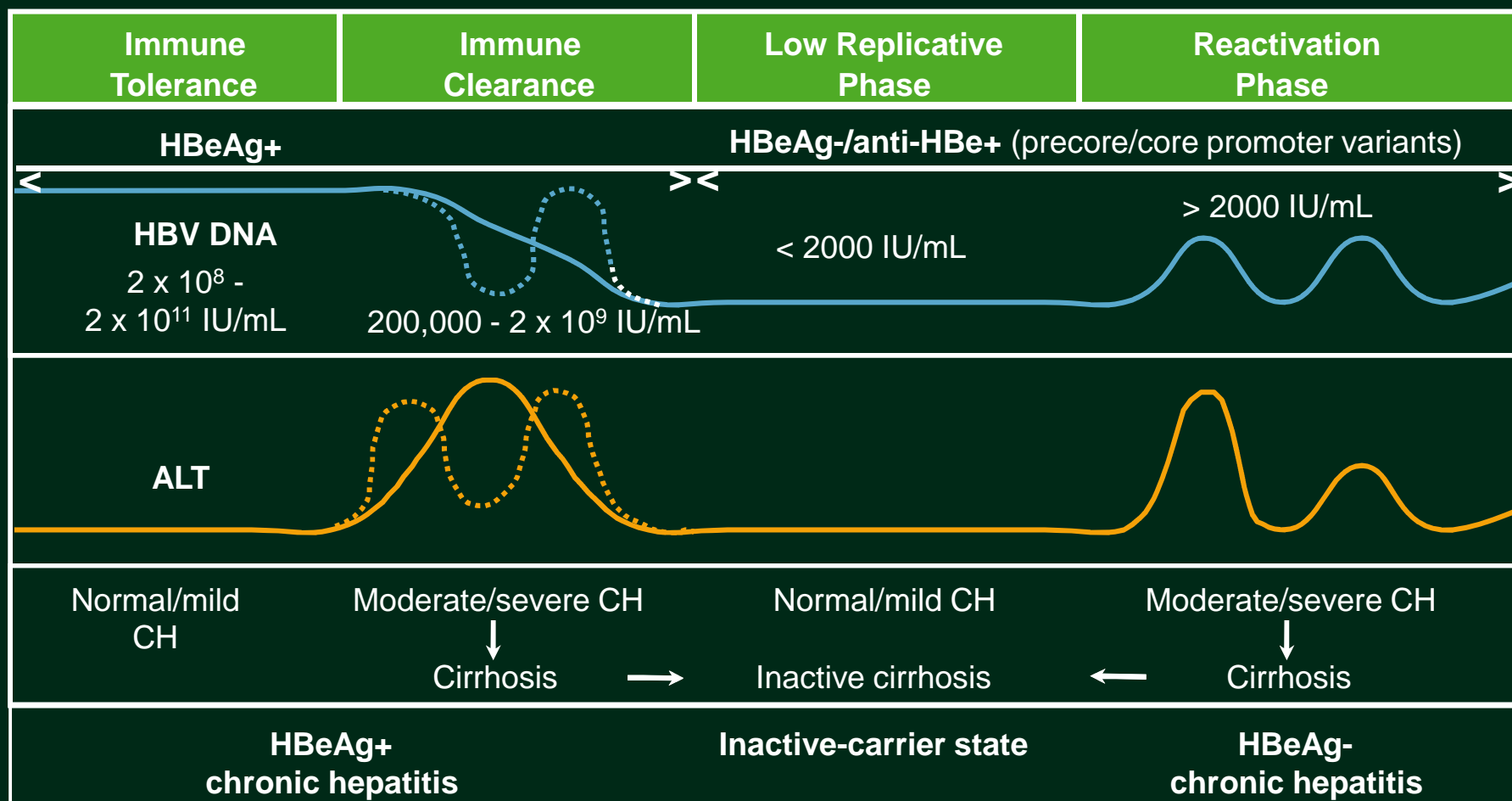
- 49 yo Caucasian male
- 3 week h/o fatigue
- **No risk factors** for recent HBV acquisition
- PE: No signs of advanced liver disease.
- ALT 725 IU/L, total bilirubin 1.7 mg/dL, INR 1.2
- **Platelet count 145,000/mm³**
- HBsAg +, Anti-HBs -, Anti-HBc IgM +, Anti-HCV -
- HBeAg +, HBV DNA 64,000 IU/mL
- U/S Abdomen: **Coarse echotexture, Spleen 15 cm**

**Assessing Patients with
chronic hepatitis B for
Treatment Candidacy:
To Treat or Not to Treat?**

Case 3: Patient History

- 40-yr-old Filipino male
- ALT 28 IU/L
- HBsAg positive, HBeAg positive
- Serum HBV DNA 60,000,000 IU/mL
- Negative viral serologies for hepatitis A and C and HIV
- Abdominal ultrasound without any significant abnormalities
- Previous medical history noncontributory
- No family history of liver disease
- No tobacco use; EtOH: 3-4 drinks/wk (wine)

Phases of Chronic HBV Infection



Slide courtesy of A. S. F. Lok, MD.

Case 3: Patient History

- 40-yr-old Filipino male
- ALT 28 IU/L
- HBsAg positive, HBeAg positive
- Serum HBV DNA 60,000,000 IU/mL
- Negative viral serologies for hepatitis A and C and HIV
- Abdominal ultrasound without any significant abnormalities
- Previous medical history noncontributory
- No family history of liver disease
- No tobacco use; EtOH: 3-4 drinks/wk (wine)

For Discussion: How Would You Classify His Chronic Hepatitis B Infection?

- A. Immune tolerance
- B. Immune clearance
- C. Chronic carrier
- D. Reactivation

Case 3: Further Workup

- 6 mos later, ALT level increased to 34 IU/L and patient agreed to a liver biopsy
 - Liver biopsy showed grade 1 inflammation and stage 1 fibrosis
- The patient continued to be monitored q6 mos
- 2 yrs later, ALT level was 92 IU/L and HBV DNA (PCR) level was 48,000,000 IU/mL
- HBV serology repeated
 - HBeAg positive, anti-HBe antibody negative

For Discussion: How Would You Classify His Chronic Hepatitis B Infection?

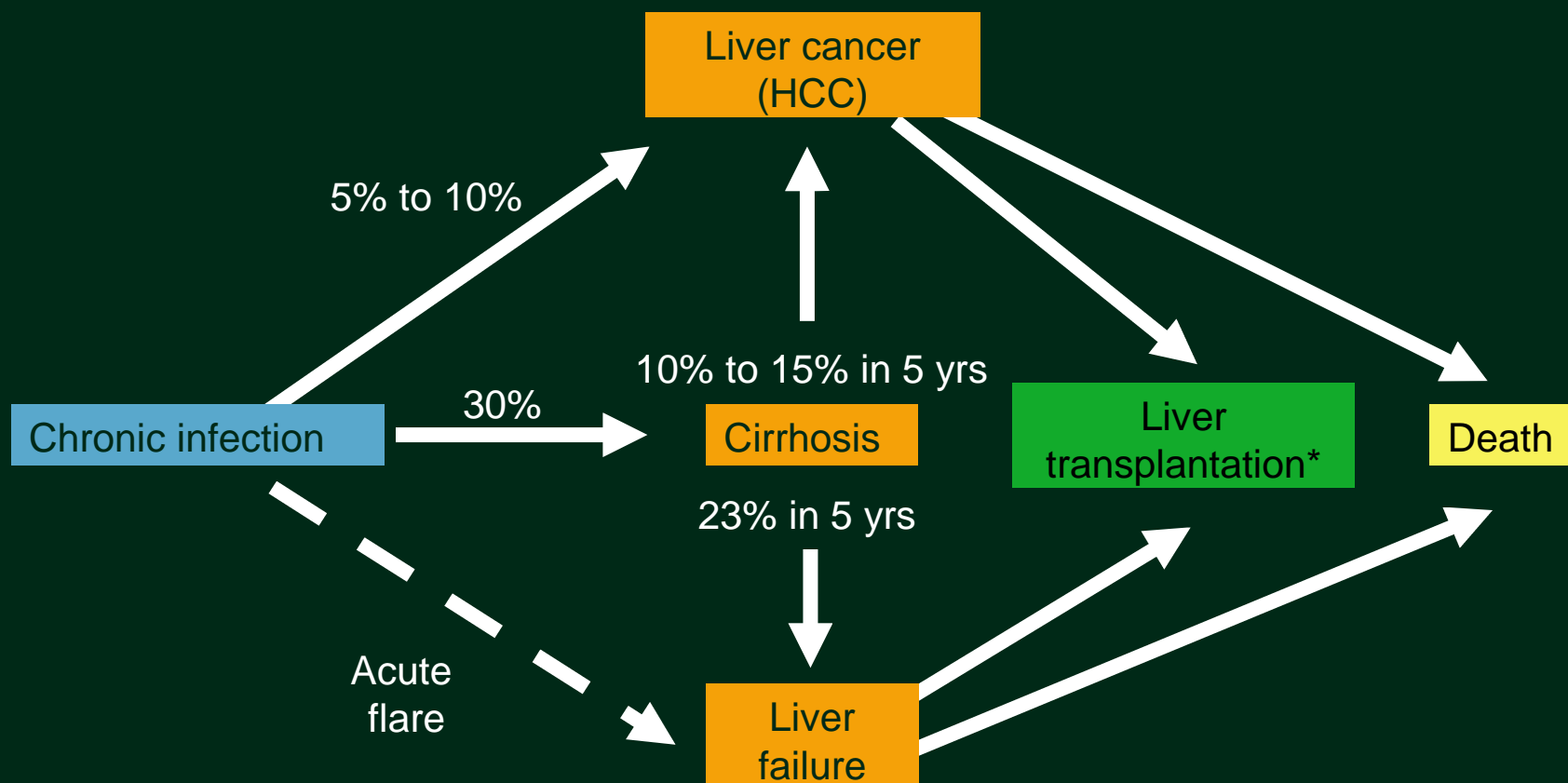
- A. Immune tolerance
- B. Immune clearance
- C. Chronic carrier
- D. Reactivation

For Discussion: Should We Start Therapy in This Patient?

A. Yes

B. No

Natural History of HBV: Directly Related to HBV DNA Level



*HBV is the 6th leading cause of liver transplantation in the United States.

Fattovich G, et al. Gastroenterology. 2004;127:S35-S50. Seeff LB, et al. Hepatology. 2001;33:455-463.
Torresi J, et al. Gastroenterology. 2000;118:S83-S103. Fattovich G, et al. Hepatology. 1995;21:77-82.

Who Should Be Treated?

- Not a question of who to treat, but when: treat now or monitor and treat later when indicated
- All HBV carriers are potential treatment candidates
- A patient who is not a treatment candidate now can be a treatment candidate in the future
 - Changes in HBV replication status and/or activity/stage of liver disease
 - Availability of new or improved treatments

Determining Treatment Candidacy for Chronic Hepatitis B: Guidelines

Guidelines	HBeAg Positive		HBeAg Negative	
	HBV DNA, IU/mL	ALT	HBV DNA, IU/mL	ALT
AASLD 2009 ^[1]	> 20,000	> 2 x ULN or positive biopsy*	≥ 20,000	≥ 2 x ULN or positive biopsy*
EASL 2009 ^[2]	> 2000	> ULN	> 2000	> ULN
APASL 2008 ^[3]	≥ 20,000	> 2 x ULN	≥ 2000	> 2 x ULN
NIH Consensus Conference 2009 ^[4]	> 20,000	> 2 x ULN or positive biopsy*	≥ 20,000	≥ 2 x ULN or positive biopsy*

*Moderate/severe inflammation or significant fibrosis.

- Expert guidelines also published with recommendations specific for HBV management in US^[5] and more recently for Asian Americans^[6]
 - Some key differences between these guidelines

1. Lok AS, et al. Hepatology. 2009;50:661-662. 2. EASL. J Hepatol. 2009;50:227-242. 3. Liaw YF, et al. Hepatol Int. 2008;3:263-283. 4. Degerek B, et al. Hepatology. 2009;S129-S137. 5. Keefe EB, et al. Clin Gastroenterol Hepatol. 2008;6:1315-1341. 6. Tong MJ, et al. Dig Dis Sci. 2011;56:3143-3162.

Case 4: Patient History

- 47-yr-old woman, born in Korea, came to the US at 35 yrs of age, recently found to be HBsAg positive during life insurance checkup
- No previous history of jaundice or acute hepatitis
- No symptoms
- Only medical problem: mild hypertension
- Family history
 - No known history of hepatitis B or liver cancer
 - Husband and 2 sons aged 20 and 25 yrs not yet tested for HBV

Case 4: Current Presentation

- Exam: normal, no jaundice or hepatosplenomegaly
- Labs
 - Hb 14 g/dL, WBC 5200 cells/mm³, platelets 142,000 cells/mm³
 - AST 11 IU/L, ALT 12 IU/L
 - Alb 4.4 g/dL, alk phos 105 IU/L, T bil 0.8 mg/dL
 - AFP 4.3 ng/mL
 - HBsAg positive, HBeAg negative, anti-HBe positive
 - HBV DNA 110 IU/mL
- Ultrasound
 - Liver normal size and texture with no mass, borderline splenomegaly

For Discussion: What Would You Recommend for This Patient?

- A. Start treatment now
- B. Order liver biopsy; start treatment if cirrhosis confirmed
- C. Observe, repeat labs q3 mos, start treatment if ALT/HBV DNA increase
- D. Reassure and discharge patient

Inactive Carrier State vs HBeAg-Negative Chronic Hepatitis B

- Inactive carrier state
 - HBeAg negative
 - Persistently normal ALT
 - Serum HBV DNA persistently undetectable or < 2000 IU/mL
- Serial follow-up necessary to differentiate inactive carriers from patients with HBeAg-negative chronic hepatitis B and intermittently normal ALT

Case 4: Follow-up

- Repeat labs

Time Point	Platelet Count, cells/mm ³	AST, IU/L	ALT, IU/L	HBV DNA, IU/mL
Mo 3	154,000	25	29	45
Mo 6	148,000	35	41	1180
Mo 9	137,000	42	59	7375

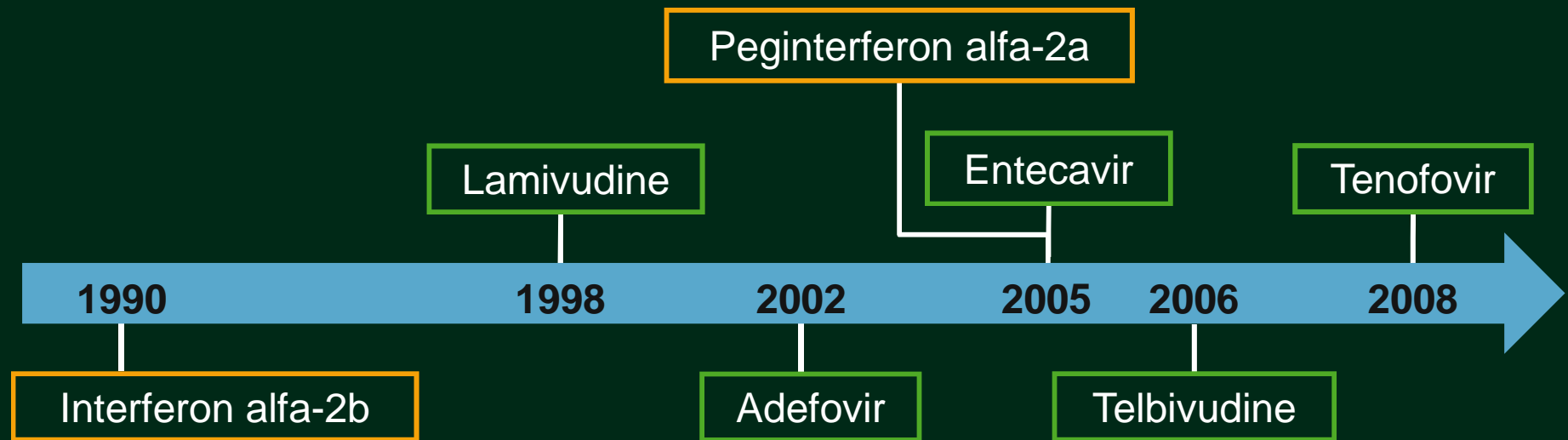
For Discussion: What Would You Recommend for This Patient at This Time?

- A. Start treatment
- B. Liver biopsy
- C. Continue to observe

Case 4: Management Decisions

- Liver biopsy performed
 - Mild inflammation, bridging fibrosis
- Oral antiviral therapy started

HBV Treatment Landscape in 2012

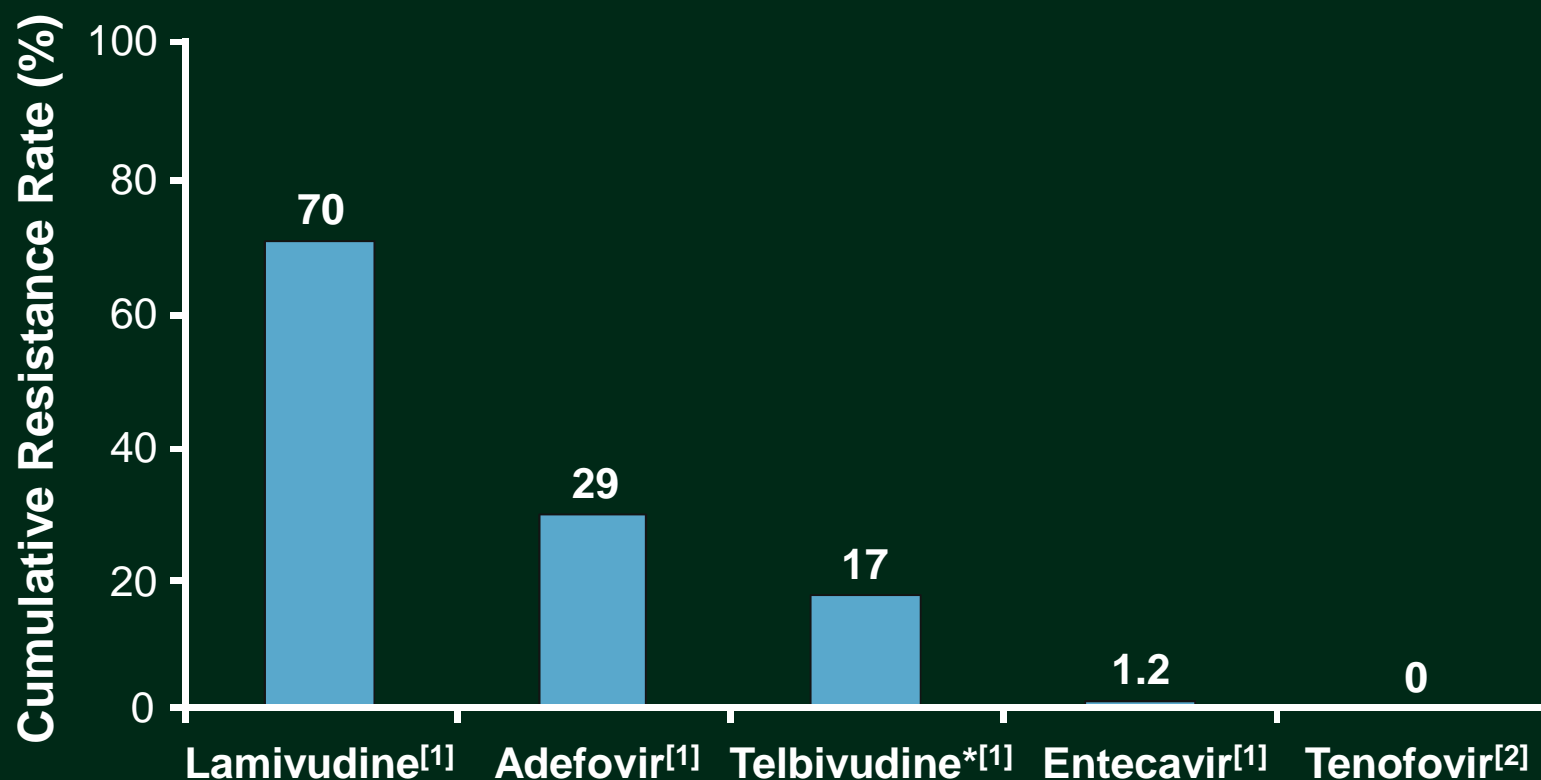


Current Guideline Recommendations for First-line Therapy

- Peginterferon alfa-2a
- Entecavir
- Tenofovir

EASL. J Hepatol. 2009;50:227-242. Liaw YF, et al. Hepatol Int. 2008;2:263-283.
Lok AS, et al. Hepatology. 2009;50:661-662.

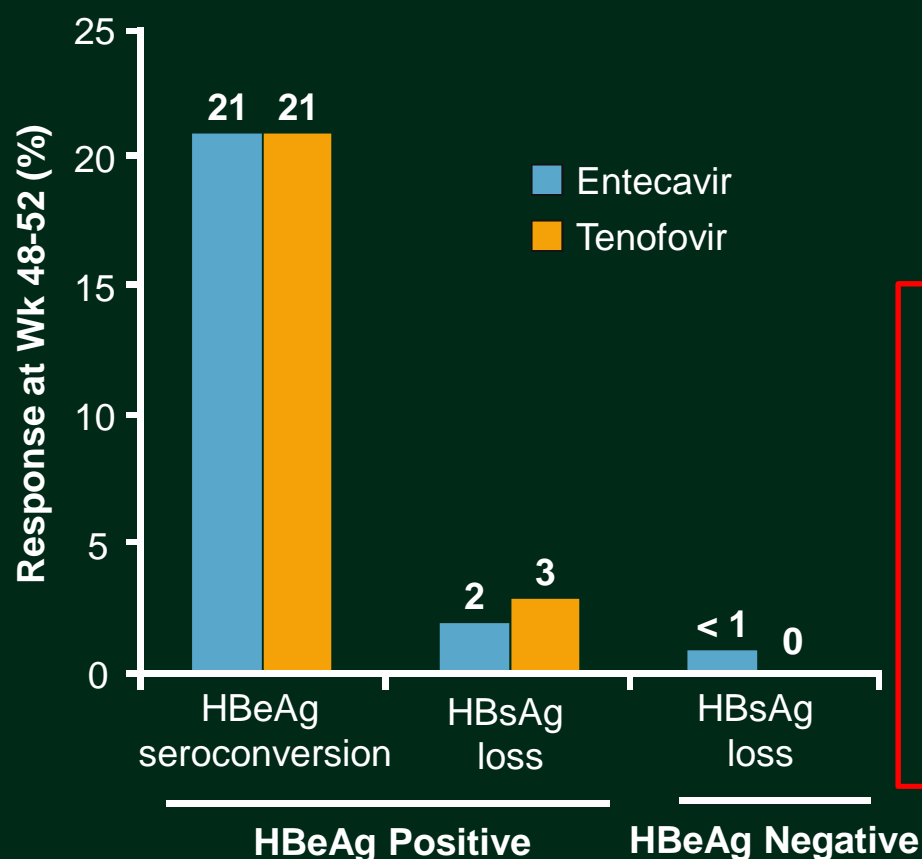
5-Yr Rates of Resistance With Oral Agents in Nucleos(t)ide-Naive Patients



*Telbivudine rate determined at Yr 2.

1. EASL. J Hepatol. 2009;50:227-242. 2. Marcellin P, et al. AASLD 2011. Abstract 1375.

Selection of Entecavir vs Tenofovir: Either Is an Excellent Choice for Most Patients



Parameter	Entecavir	Tenofovir
Log HBV DNA ↓ at Wk 48-52		
▪ HBeAg positive	6.9	6.2
▪ HBeAg negative	5.0	4.6
Genotypic resistance, %		
▪ NA naive	1.2 (Yr 5)	0 (Yr 3)
▪ Lamivudine experienced	51 (Yr 5)	NR
Pregnancy rating	Class C	Class B
AEs	None	Renal toxicity; ↓ BMD

When to Consider PegIFN

- Favorable predictors of response^[1,2]
 - Low HBV DNA*
 - High ALT*
 - Genotype A or B > C or D^[3-5]
 - Not advanced disease
- Specific patient demographics^[1,2]
 - Generally young people
 - Young women wanting pregnancy in near future
 - Absence of comorbidities
- Patient preference^[1,2]
- Concomitant HCV infection

*Also predictive of response to nucleos(t)ide analogues.

1. Lok AS, et al. Hepatology. 2009;50:661-662. 2. Lok AS. Hepatology. 2010;52:743-747. 3. Janssen HL, et al, Lancet. 2005;365:123-129. 4. Lau GK, et al. N Engl J Med. 2005;352:2682-2695. 5. Flink HJ, et al. Am J Gastroenterol. 2006;101:297-303.